

## His Corrective Pacing or Biventricular Pacing for Cardiac Resynchronization in Heart Failure

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Biventricular pacing (BiV) is established as the primary modality to achieve cardiac resynchronization therapy (CRT), although non-response rates approach 30-40% (1). His bundle pacing has emerged as a viable option for CRT with physiological restoration of electrical synchrony by circumventing proximal conduction disease (2-4). The frequency in which His bundle pacing can correct left bundle branch block patterns (LBBB) in an unselected heart failure population is not known, and no prospective trials comparing BiV-CRT versus His bundle pacing in lieu of an LV lead for CRT (His-CRT) have been performed to date. The His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy (His-SYNC) pilot trial was an investigator-initiated, prospective, randomized controlled trial that aimed to assess the feasibility and efficacy of His-CRT as a first-line strategy compared to BiV-CRT.

The study was conducted between May 2016 and June 2018 at 7 centers, and the University of Chicago served as the Study Coordinating Site (NCT02700425). Approval by the local institutional review board was obtained at each center, and patients were blinded to treatment allocation. Eligible patients aged >18 years meeting guideline indications for CRT were considered for inclusion. Patients were centrally randomized to His-CRT or coronary sinus lead for BiV-CRT with routine implantation techniques (1).

As the trial sought to compare two strategies for CRT, crossover was mandated in patients assigned to His-CRT who did not achieve QRS narrowing by >20%, QRS width of  $\leq 130$  ms, or who demonstrated high correction thresholds ( $>5V@1$  ms). Crossover was permitted in patients randomized to BiV-CRT in whom an LV lead could not be placed. LV lead delivery into the anterior interventricular or middle cardiac veins was discouraged. The primary outcomes of the trial were change in QRS duration, improvement in LVEF at 6 months, and time to cardiovascular hospitalization or death at 12 months.

Among 41 patients enrolled ( $64\pm 13$  yrs, 38% female, LVEF 28%, 65% with coronary artery disease, QRS width  $168\pm 18$  ms [LBBB pattern=35, RBBB=2, paced=3]), 21 were randomized to His-CRT and 20 to BiV-CRT. One patient withdrew prior to implant in the BiV-CRT group. Baseline characteristics revealed no differences except that LVEF was significantly lower among His-CRT (median 26.3% [21.3-28.3%] compared to BiV-CRT (30.5% [27.1-33.9%],  $p=0.011$ ). Crossover occurred in 48% of His-CRT and 26% of BiV-CRT. The most common reasons for crossover from His-CRT was inability to correct QRS ( $n=5$ ) and suboptimal venous anatomy ( $n=4$ ) in BiV-CRT.

By intention-to-treat (ITT) analysis, significant reduction in QRS duration was observed with His-CRT ( $172\pm 16$  ms to  $144\pm 30$  ms;  $p=0.002$ ), but not BiV-CRT ( $165\pm 18$  ms to  $152\pm 30$  ms;  $p=0.11$ ), although between-group differences were not significant ( $p=0.42$ ). At a median follow-up of 6.2 months, improvements in LVEF relative to baseline were seen in both His-CRT (26.3% to 31.9%,  $p<0.001$ ) and BiV-CRT patients (30.5% to 34.0%,  $p<0.001$ ). His-CRT was not superior to BiV-CRT with regard to LVEF improvement (median +9.1% [5.0-14.4%] vs. +5.2 [1.5-11.3%],  $p=0.33$ ) or rate of echocardiographic response  $\geq 5\%$  (76% vs. 53%,  $p=0.13$ ). Overall event rates were low (6 cardiovascular hospitalizations, 2 deaths), with no differences observed between groups (**Figure**). No His or LV lead dislodgements were observed during study follow-up.

QLV was reported in 20 of 24 patients receiving BiV across both arms (mean  $131\pm 29$  ms; mean QLV ratio  $0.80\pm 0.19$ ). Compared to those randomized to BiV-CRT, patients assigned to His-CRT had higher pacing thresholds (median 1.7 V versus 0.9 V,  $p=0.046$ ), but not pulse width (median 1 ms versus 0.5 ms,  $p=0.45$ ). His corrective capture thresholds remained stable in up to 12 months of follow-up.

In this first randomized pilot trial, His-CRT did not demonstrate significant improvements in electrocardiographic or echocardiographic parameters as compared to BiV-CRT. This study was underpowered to detect differences less than 10% between groups and a type II error cannot be excluded. Importantly, ITT analysis in the presence of high crossover rates cannot directly assess treatment efficacy. Longer helices, deflectable sheaths with septal orientation, and intra-septal fixation are likely to improve His correction rates and stability of thresholds. In patients that required crossover from His-CRT, one-half of patients exhibited nonspecific intraventricular conduction delay (IVCD), which is unlikely to be corrected by His-CRT (4). Improved patient selection may decrease crossover rates and larger prospective studies may be useful to assess for smaller differences in effect size between CRT modalities.

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**Figure Legend**

**Figure.** Reduction in QRS duration and echocardiographic response by intention-to-treat analysis of patients randomized to BiV-CRT versus His-CRT.

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